REMARKS

Claims 1-4, 15 and 16 are pending in the above-referenced application. Claims 5-14 are withdrawn from consideration as being drawn to non-elected inventions. Claims 1-4, 15 and 16 have been rejected under 35 U.S.C. § 112, first paragraph. In addition, the Examiner has objected to the specification as being unclear in the recitation of "transforming growth factor-χ (TGF-β)" and for failing to provide proper antecedent basis for the claimed subject matter.

Claims 1, 2, 4 and 15 have been amended. In particular, claim 1 has been amended to address the Examiner's concerns and to recite fusion proteins that include amino acids 20-41 of SEQ ID NO: 9 with a "*functional* heparan sulphate attachment sequence *having the amino acid sequence SGSG*, or amino acids 20-41 of SEQ ID NO: 9 with *at least one* conservative amino acid substitution *occurring outside of the functional heparan sulfate attachment sequence.*" Support for a "functional" heparan sulphate attachment sequence is found throughout the specification. For example, support for this term can be found specifically at page 4, lines 3-4; page7, lines 20-24; page 11, lines 23-26; page 27, lines 24-29; and page 34, lines 7-9. Support for the phrase "at least one conservative amino acid substitution" can be found, for example, at page 5, lines 11-14. Support for the phrase "conservative substitutions occurring outside the functional heparan sulphate attachment sequence" can be found throughout the specification, for example, at page 71, line 8 through page 74, line 10, and more specifically at page 74, lines 5-10. Claims 2, 4 and 15 have been amended to correct obvious clerical and typographical errors. The specification has also been amended in response to the Examiner's objections and to correct an obvious typographical error. No new matter has been added by either the claim amendments or the specification amendments.

Amendment of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and has been done solely to more particularly point out and distinctly claim the invention to expedite prosecution of this application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Applicants enclose herewith a petition for a 3-month extension of time in which to file this response, together with the appropriate fee.

Objections to the Specification

The specification has been objected to as being unclear in the recitation of "transforming growth factor-χ (TGF-β)." Applicants thank the Examiner for pointing out this error and have amended the specification to read "transforming growth factor-β (TGF-β)."

The specification is also objected to as failing to provide proper antecedent basis for a heparan sulfate attachment site comprising amino acids 20-41 of SEQ ID NO: 9, or fusion proteins thereof. Applicants have taken the suggestion of the Examiner and amended the specification to disclose the 22 amino acid polypeptide of the claimed fusion protein in the paragraph bridging pages 48-50.

Applicants believe these amendments satisfy the Examiner's concerns and kindly request reconsideration and withdrawal of these objections.

Rejections of claims 1-4, 15 and 16 under 35 U.S.C. § 112, first paragraph

Enablement:

Claims 1-4, 15 and 16 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention to the full extent of the claims. The Examiner states on page 4, lines 11-16, of the Office Action:

> [t]he specification, while being enabling for fusion polypetides comprising the residues 20-41 of SEQ ID NO: 9, and for fragments thereof that comprise the Xac-Z-Ser-Gly-Ser-Gly heparan sulfate (HS) binding sequence (SGSG sequence) described on page 4 of the specification, the claims are not enabling for any peptide of residues 20-41 of SEQ ID NO: 9 with any number of conservative substitutions therein. This is especially true for substitutions in the SGSG sequence.

The Examiner further states on page 6, lines 1-10:

> As the applicant has taught only the SGSG sequence as a heparan sulfate-binding site, the applicant is not enabled for any peptide according to the claims that can

> bind HS, other than those comprising the SGSG sequence. . . . Due to the breadth of the claims, the unpredictability of the art, and the lack of guidance provided by the applicant, and because the utility of the claimed fusion protein depends on the presence of the heparan sulphate, the applicant is not enabled for claims to a fusion protein that can comprise any number of substitutions. Nor is the applicant enabled for peptides with even one substitution in the SGSG sequence.

Although Applicants respectfully disagree with the basis of this rejection, in order to expedite prosecution of the present application, Applicants have amended independent claim 1 to comply with the Examiner's suggestions. As amended, claim 1 recites, inter alia, a fusion protein with a first polypeptide portion comprising a "*functional* heparan sulphate attachment sequence *having the amino acid sequence SGSG*, or amino acids 20-41 of SEQ ID NO: 9 with *at least one conservative amino acid substitution occurring outside of the functional heparan sulfate attachment sequence.*" Thus, amended claim 1 speaks to fusion proteins having a syndecan polypeptide with a functional heparan sulphate attachment sequence, as well as a syndecan polypeptide with at least one conservative amino acid substitution occurring *outside of the functional heparan sulphate attachment sequence,* i.e., the substitutions are not made within the SGSG sequence. Applicants believe these amendments fully address the Examiner's concerns, and respectfully request reconsideration and withdrawal of the rejection.

Support for the above amendments can be found throughout the specification. The specification describes, for example, how to make at least one conservative substitution at page 10. Conservative substitutions are described by Applicants as those which have no effect on the biological activity of the molecule, and the amino acids are structurally similar. The specification states at page 10:

> it is reasonable to expect that an isolated replacement of a leucine with an isoleucine or valine, an aspartate with a glutamate, a threonine with a serine, or a similar replacement of an amino acid with a structurally related amino acid (i.e. conservative mutations) will not have a major effect on the biological activity of the resulting molecule.

Applicants go on to describe the types of conservative substitutions that can be made, and group families of amino acids with similar physiochemical characteristics, such as size, charge,

and polarity/non-polarity and describe these as "conservative" (see page 11, first full paragraph). Applicants further state that these substitutions should result in a polypeptide portion with a *functional* heparan sulphate attachment sequence and describe at great length how to test for functionality, assessed by the ability of the polypeptide with the heparan attachment sequence to attach a GAG chain. For example, at page 11, lines 23-30, Applicants state that:

> Whether a change in the amino acid sequence of a peptide results in a functional heparan sulfate attachment sequence can readily be determined by assessing the ability of the corresponding DNA encoding the peptide to produce this peptide in a form containing a glycosaminoglycan chain when expressed by eukaryotic cells. Examples of this process are described later in detail. If attachment of glycosaminoglycan chains occurs, the replacement is immaterial, and the molecule being tested is equivalent to those specifically described above. Peptides in which more than one replacement has taken place can readily be tested in the same manner.

Applicants provide ample guidance on how to make syndecan sequences containing heparan sulfate attachment sites in Section III, *Expression of Recombinant Syndecans and Syndecan homologs*, beginning on page 27. Applicants also describe a number of techniques to test for *functional* attachment sites using panning assays (*see* Section IV, beginning on page 33, and Example 14).

Applicants specification also provides the amino acid sequence of SEQ ID NO: 9 at page 49, as well as Table I, on page 9, which identifies the various codons that encode for each amino acid. Using the amino acids sequence of SEQ ID NO: 9 (focusing specifically on residues 20-41), and using Table I, as well as the description of conservative amino acid families, and the description of site directed mutagenesis described in Examples 9 and 10, the skilled artisan would readily be able to generate a polypeptide with at least one substitution. The substitution may be at any location outside the SGSG sequence. The effect of the mutation can be tested using the methodology described in Example 14. Based on the ample guidance and teachings provided by Applicants specification, the skilled artisan would readily be able to generate a polypeptide with at least one conservative mutation in SEQ ID NO: 9.

Accordingly, Applicants specification provide ample guidance on how to make fusion proteins with a polypeptide portion having at least one substitution.

With regard to the Examiner's concern that while active sites are sometimes tolerant to conservative substitutions not all conservative substitutions will be "allowed," Applicants have limited claim 1 to fusion proteins comprising at least one conservative substitution *outside* of the functional heparan sulphate attachment sequence (SGSG). Similarly, with regard to the Examiner's concern that sequences with 70 or 80 percent or less identity with the claimed sequence may not retain the ability to bind HS, Applicants have limited the claims to fusion proteins comprising *amino acid sequence SGSG*. Applicants believe these amendments obviate the Examiner's concerns, and respectfully request reconsideration and withdrawal of the rejection.

Written Description

Claims 1-4, 15 and 16 have been rejected under 35 U.S.C § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner states on page 7, lines 13-20:

> [T]he teachings of the specification teach that the SGSG sequence identified above is required for [heparan sulfate] binding. Page 4. There is no indication of other sequence, or modified versions of this sequence, that would also be capable of binding to heparan sulfate. Thus, while the application provides descriptive support for heparan sulfate attachment sequences comprising SEQ ID NO: 9, or variants thereof maintaining the SGSG sequence, the application does not provide support for the claims to the extent that they read on any variant of SEQ ID NO: 9 that does not comprise the SGSG sequence.

Although Applicants respectfully disagree with the basis of this rejection, in order to expedite prosecution of the present application, Applicants have amended independent claim 1. Specifically, claim 1 as amended requires a "*functiona* heparan sulphate attachment sequence

having the amino acid sequence SGSG, or amino acids 20-41 of SEQ ID NO: 9 with *at least one conservative amino acid substitution occurring outside of the functional heparan sulfate attachment sequence.*" Thus, amended claim 1 speaks to fusion proteins that comprise a syndecan polypeptide with a functional heparan sulphate attachment sequence comprising the SGSG sequence, as well as a syndecan polypeptide with at least one conservative amino acid substitution occurring *outside of the functional heparan sulphate attachment sequence,* i.e., the substitutions are not made within the SGSG sequence. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejections of claim 3 under 35 U.S.C. § 112, first paragraph

Enablement

Claim 3 is further rejected under 35 U.S.C. § 112, first paragraph. The Examiner states on page 7, lines 21-24, that "the specification, while enabling for fusion proteins comprising residues 20-41 of SEQ ID NO: 9 that bind to chondroitin sulfate in addition to heparan sulfate, *does not reasonably provide enablement for any variant of the sequence that* ***maintains chondroitin sulfate binding activity***." The Applicants respectfully traverse this rejection.

As discussed above, Applicants have amended claim 1 to require that the fusion protein comprise a first polypeptide with a "*functional* heparan sulphate attachment sequence" (i.e., comprising amino acid sequence SGSG), which has a heparan sulfate glycosaminoglycan chain attached thereto. The fusion protein also has a second polypeptide portion with an amino acid sequence from a protein which does not naturally have a covalently linked heparan sulphate glycosaminoglycan chain. Thus, claim 1 states that "the heparan sulphate glycosaminoglycan chain attached to the first polypeptide portion modifies the function of the second polypeptide portion." In other words, it is the *heparan* sulphate attachment sequence that influences the functionality of the fusion protein (i.e. any variants containing conservative amino acid substitutions must retain *heparan* sulphate binding activity), regardless of any chondroitin sulfate moiety or binding activity.

Claim 3, which depends from claim 1, recites a fusion protein "*further comprising* at least one *chondroitin sulfate* ***glycosaminoglycan***." The specification teaches on page 70, lines 5-16, that:

> [w]hile the desirable binding activities of [the smallest truncations of syndecan-1] reside in the heparan sulfate chains, for most applications the presence of the chondroitin sulfate chains on constructions of this invention would not adversely affect [the] activities of these products (and in some cases could enhance functionality)". . . . [A]ttachment sites (serine 207 and 217) . . . are understood to contain chondroitin sulfate chains only. The hypothesis that the attachment site at serine 37 also specifies chondroitin sulfate attachment has been demonstrated by site directed mutants.

Contrary to the Examiner's assertion, claim 3 does not require that a variant protein "***maintains chondroitin sulfate binding activity***." Rather than requiring chondroitin sulfate binding activity, claim 3 simply states that the fusion protein, in addition to a functional heparan sulphate attachment sequence (with an attached heparan sulphate glycosaminoglycan chain), also comprises at least one chondroitin sulfate glycosaminoglycan. As discussed above, the specification describes (i.e., enables) such fusion proteins.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection of claim 3 under 35 U.S.C. § 112, first paragraph, for lack of enablement.

Written Description

Claim 3 is also rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner states that "the claims reads on any fusion protein comprising SEQ ID NO: 9 that is able to bind to chondroitin sulfate" and has "identified the claimed genus only by identification of a function, and [does] not provide any structural requirement shown, or known, to correlate with the chondroitin sulfate binding function" (Office Action page 9, lines 5-6 and 15-17, respectively). As discussed above, claim 3 requires that the fusion protein of claim 1 "*further comprise* at least one *chondroitin sulfate glycosaminoglycan*." Thus, rather than requiring chondroitin sulfate binding activity, claim 3 an additional structural requirement, namely the presence of a chondrointin sulfate

glycosaminoglycan.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection of claim 3 under 35 U.S.C. § 112, first paragraph, for lack of a sufficient written description.

CONCLUSION

It is believed that the amended claims are in condition for allowance, and reconsideration is respectfully requested for all the reasons set forth above. The Examiner is urged to telephone the undersigned Attorney for Applicants in the event that such communication is deemed to expedite prosecution of this matter.

Respectfully submitted,

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